Remarks

Reconsideration of this Application is respectfully requested. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 2 and 3 were rejected under 35 U.S.C. § 102(a) as anticipated by Vito, P., *et al.*, *J. Biol. Chem. 271:*31025-28.[1] Applicants respectfully traverse.

"'For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference.'" *In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990)(citing *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988)); *see also Finnigan Corp. v. United States Int'l Trade Comm'n*, 180 F.3d 1354, 1365-66, 51 USPQ2d 1001, 1008 (Fed. Cir. 1999).

Claim 2 is directed to an antibody having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF). Claim 3 is directed to a method of detecting 20 kDa PS2-CTF in a sample using this antibody.

Vito *et al.* disclose two polyclonal antisera raised against different fragments of presenilin 2 (PS2). The first of these antisera, αPS2n, was raised against a fusion protein containing amino acids 341-377 of PS2. Vito, P. *et al.*, *J. Biol. Chem. 49:*31025-28, at

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[1] Although Applicants address this rejection on the merits, Applicants reserve the right to establish that Vito *et al.*, and any other document cited by the Examiner, does not qualify as prior art.

31025 (1996). The second of these antisera, αPS2c, was raised against a peptide containing amino acids 438-448 of PS2 linked to a keyhole limpet hemocyanin. *Id.* Vito *et al.* discloses that, in addition to recognizing the fragments against which these antisera were raised, αPS2n recognizes full-length PS2, and αPS2c recognizes both full-length PS2 and ALG-3 an approximately 10 kDa fragment of the mouse homologue of PS2. *See, id.* at 31026-27. Thus, neither of these antisera are "specific only to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF)" as is recited by the claims. Therefore, neither of these antisera meet all of the limitations of either claim 2 or 3.

In response to a similar argument made in the previous reply, the Examiner has stated that claims 2 and 3 must encompass the antisera disclosed in Vito et al., αPS2n and αPS2c, because they encompass an antibody disclosed in the specification, αPS2Loop, which recognizes full-length PS2 as well as the 20 kDa PS2-CTF. This argument was presented as follows:

> However, as noted in the specification in Figure 7, panel c (described on page 10, line 10 to page 11, line 3) and Figure 8 (described on page 11, lines 4-10) the instant αPS2Loop antibody used to detect the 20 kDa PS2-CTF was also able to bind to the full-length form of PS2 (54kDa) as well as the normal PS2-CTF cleavage product of 26 kDa. The presence of the different forms of PS2 in the αPS2Loop immunoblots appears to differ based on the source of the sample (e.g., detergent resistant fraction is enriched in the 20 kDa PS2-Ctf fragment) rather than its specificity to the 20 kDa PS2-CTF.

(*See* Paper No. 15, at 3.)

However, the Examiner's argument is based on an incorrect assumption. αPS2Loop is not "[a]n antibody having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF)" and Applicants have never asserted that it is. Although αPS2Loop is used in some of the experiments described in the Application, Applicants do not contend that it is encompassed by claims 2 or 3. Rather, the Application discloses at page 37, lines 8-12, that the αPS2Loop polyclonal antisera was provided by Drs. Gopal Thanikaran and Sam Sisodin, and cites Thinakaran, G. *et al.*, *Neuron 17:*181-90 (1996).

As defined in the specification "[a]n antibody having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF)" would not bind full-length PS2. *See e.g.,* Specification at 19, lines 16-24. It is specific for a particular fragment of PS2 (PS2-CTF). Cleavage site specific antibodies and methods of making them were known by Applicants' filing date. *See, e.g.,* Fosang, A.J., *et al.*, "Development of a cleavage-site-specific monoclonal antibody for detecting metalloproteinase-derived aggrecan fragments: detection of fragments in human synovial fluids," *Biochem. J. 310*:337-343 (1995). (Submitted herewith as Exhibit A).

Thus, the αPS2n and αPS2c antisera disclosed in Vito *et al.* fall outside the scope of claims 2 and 3, and, therefore, do not anticipate either of these claims. Consequently, it is respectfully requested that the rejection under 35 U.S.C. § 102(a) of claims 2 and 3 be withdrawn.

Rejections Under 35 U.S.C. § 103

Claim 4 has been rejected under 35 U.S.C. § 103(a) as obvious over Vito *et al.*, discussed above, in view of Dalbow *et al.*, U.S. Patent No. 4,116,776. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the articles cited by the Examiner must (1) teach all of the claim limitations; MPEP § 706.02(j); (2) provide a suggestion or motivation to those of ordinary skill in the art to make the claimed transgenic mouse; and (3) reveal that one of ordinary skill would have a reasonable expectation of success in doing so; *see In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *see also* MPEP § 706.02(j) (7th Ed. July, 1998).

The cited article and patent do not meet even the first requirement. Claim 4 is directed to a diagnostic kit comprising, *inter alia*, an antibody having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF). As discussed above, Vito *et al.* discloses polyclonal antisera that are not specific to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF). Dalbow *et al.* does not remedy the deficiency in Vito *et al.* Dalbow *et al.* discloses a diagnostic test using a labeled antiserum specific to the beta-subunit of human chorionic gonadotropin, but contains no teachings regarding presenilin 2 or PS2-CTF. Therefore, Vito *et al.* and Dalbow *et al.* do not teach, or even suggest, a kit containing an antibody "having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment." Thus, they do render claim 4 obvious. Applicants respectfully request that this rejection be withdrawn.

Claim 5 has been rejected under 35 U.S.C. § 103(a) as obvious over Vito *et al.*, in view of Janeway C.A., Jr. *et al.*, Immunobiology, New York, Current Biology (1997). Applicants respectfully traverse this rejection. Claim 5 is directed to a hybridoma that produces an antibody having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF). As discussed above, Vito *et al.* discloses polyclonal antisera that are not specific to the 20 kDa presenilin 2 C-terminal fragment (PS2-CTF). Janeway *et al.* discloses general information about antibodies and their use, but nothing regarding presenilin 2 or PS2-CTF. These articles do not teach, or even suggest a hybridoma that produces an antibody having binding affinity that is specific only to the 20 kDa presenilin 2 C-terminal fragment. Therefore, Vito *et al.* and Dalbow *et al.* do not render claim 4 obvious. Consequently, Applicants respectfully request that this rejection be withdrawn.

Claims 9 and 10 have been rejected under 35 U.S.C. § 103(a) as obvious over Tanzi, R.E., *et al.*, *Neurobiol. Dis. 3:*159-168 (1996) in view of Miller, D.K. *et al.*, *Ann. New York Acad. Sci. 696:*133-148 (1993). Claims 9 and 10 are directed to a method for screening compounds that inhibit proteolytic processing of presenilin 2 in a cell. Previously, Applicants submitted a Declaration of Co-Inventors Under 37 C.F.R. § 1.132 regarding the abstract, Kim *et al.*, *Neurobiol. Aging 17:*S1555 (July 24 1996), which was cited in the section of the Tanzi *et al.* review article relating to PS2-CTF. However, the Examiner has not found this Declaration sufficient to remove Tanzi *et al.*

Applicants contend that, because Tanzi *et al.* is a review article discussing the work of a variety of groups of authors, and because the relevant portion of Tanzi *et al.* cited by the Examiner relates to experiments performed and described by the Kim *et al.* authors, the Declaration previously submitted was proper. However, in the interest of expediting prosecution, submitted herewith is another Declaration of Co-Inventors Under 37 C.F.R. § 1.132, executed by Drs. Rudolph Tanzi and Tae-Wan Kim. (The copy executed by Dr. Tanzi is attached as Exhibit B, and that executed by Dr. Kim is attached as Exhibit C). This Declaration establishes that the work discussed in Tanzi *et al.* relating to PS2-CTF is their own, and that the other co-authors of Tanzi *et al.* are not co-inventors of the above-captioned application. Thus, the Declaration removes Tanzi *et al.* as a reference under 35 U.S.C. § 102(a).

According to the Examiner, Miller *et al.* teaches "a method of screening compounds that inhibit the proteolytic processing of Interleukin 1β by the cystein protease, Interleukin β converting enzyme (ICE)." (Paper No. 10, at 5.) However, Miller *et al.* discloses nothing regarding presenilin 2 or screening for compounds that inhibit the proteolytic processing of presenilin 2. Thus, Miller *et al.* does not render claim 8 or 9 obvious. Therefore, Applicants respectfully request that this rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be

withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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